(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 August 2002 (22.08.2002)

PCT

(10) International Publication Number
WO 02/064080 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/IB02/00447

(22) International Filing Date: 13 February 2002 (13.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/268,821 14 February 2001 (14.02.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

of inventorship (Rule 4.17(iv)) for US only

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MATRIX METALLOPROTEINASE INHIBITORS

(57) Abstract: Compounds are provided that bind allosterically to the catalytic domain of MMP-13 and comprise a hydrophobic group, first and second hydrogen bond acceptors and at least one, and preferably both, of a third hydrogen bond acceptor and a second hydrophobic group. Cartesian coordinates for centroids of the above features are defined in the specification. When the ligand binds to MMP-13, the first, second and third (when present) hydrogen bond acceptors bond respectively with Thr245, Thr247 and Met 253, the first hydrophobic group locates within the S1' channel of MMP-13 and the second hydrophobic group (when present) is relatively open to solvent. The compounds specifically inhibit the matrix metalloproteinase-13 enzyme and thus are useful for treating diseases resulting from tissue breakdown, such as heart disease, multiple sclerosis, arthritis, atherosclerosis, and osteoporosis.

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CLAIMS

1. A compound that binds allosterically to MMP-13 and that comprises first and second hydrophobic groups and first and second hydrogen bond acceptors, wherein:

(a) the relative positions of centroids of the above features are defined by the following Cartesian coordinates in Å:

(i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;

(ii) second hydrogen bond acceptor, 5.08, 2.23, 0.00;

(iii) first hydrophobic group, –1.52, -3.06, -0.23;

(iv) second hydrophobic group, 9.07, 0.00, 0.00; and

(b) tolerances in the positions of the hydrophobic groups and the hydrogen bond acceptors are ± 1.0 Å and ± 1.5 Å respectively.

2. The compound of claim 1, wherein the first hydrophobic group contains a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a 5- or 6-membered monocyclic aromatic group which may contain one or more heteroatoms and which may be 4-substituted or 3,4-disubstituted, but which is of width (including substituents) less than 4.0 Å.

3. The compound of claim 2, wherein the pi-system of the aromatic ring is electron rich.

4. The compound of claim 1, wherein first hydrophobic group, is linked by a first linker chain which is three atoms long to a first 5- or 6-membered ring of the scaffold, the first linker chain atom adjacent to said first scaffold ring forming part of the first hydrogen bond acceptor.

5. The compound of claim 4, wherein the first linker chain has a methylene group located adjacent to the hydrophobic group.

6. The compound of claim 4, wherein the scaffold further comprises a second scaffold ring fused to the first scaffold ring at locations two and three ring atoms distant from the junction between the first scaffold ring and the first linker chain, and the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is two positions distant from said junction forms part of the second hydrogen bond acceptor.

7. The compound of claim 6, wherein the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is three positions distant from said junction has a substituent which is a single atom or is a methyl group.

8. The compound of claim 1, wherein the second hydrophobic group is a 5- or 6-membered aromatic ring which may contain one or several heteroatoms, a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a planar saturated or unsaturated system.

9. A compound that binds allosterically to MMP-13 and that comprises a hydrophobic group and first, second and third hydrogen bond acceptors, wherein:

(a) the relative positions of centroids of the above features are defined by the following Cartesian coordinates in Å:

(i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;

(ii) second hydrogen bond acceptor, 5.08, 2.23 ,0.0;

(iii) third hydrogen bond acceptor, 7.15, 0.80, 0.00;

(iv) first hydrophobic group, –1.52,-3.06, -0.23; and

(b) tolerances in the positions of the hydrophobic group and the hydrogen bond acceptors are ± 1.0 Å and ± 1.5 Å respectively.

10. The compound claim 9, wherein the first hydrophobic group contains a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a 5- or 6-membered monocyclic aromatic group which may contain one or more heteroatoms and which may be 4-substituted or 3,4-disubstituted, but which is of width (including substituents) less than 4.0 Å.

11. The compound of claim 10, wherein the pi-system of the aromatic ring is electron rich.

12. The compound of claim 10, wherein first hydrophobic group, is linked by a first linker chain which is three atoms long to a first 5- or 6-membered ring of the scaffold, the first linker chain atom adjacent to said first scaffold ring forming part of the first hydrogen bond acceptor.

13. The compound of claim 12, wherein the chain has a methylene group located adjacent to the hydrophobic group.

14. The compound of claim 12, wherein the scaffold further comprises a second ring fused to the first scaffold ring at locations two and three ring atoms distant from the junction between the first scaffold ring and the chain, and the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is two positions distant from said junction forms part of the second hydrogen bond acceptor.

15. The compound of claim 14, wherein the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is three positions distant from said junction has a substituent which is a single atom or is a methyl group.

16. The compound of claim 14, wherein the second scaffold ring is 6-membered and the atom of the second scaffold ring that is two positions distant from the atom that forms part of the second hydrogen bond acceptor forms part of the third hydrogen bond acceptor.

17. The compound of claim 14, wherein the second scaffold ring is 6-membered and a third scaffold ring is fused to the second scaffold ring at those atoms of the second scaffold ring which are two and three positions distant from

the atom that forms part of the second hydrogen bond acceptor, an atom of the third scaffold ring forming part of the third hydrogen bond acceptor.

18. A compound that binds allosterically to MMP-13 and that comprises first and second hydrophobic groups and first, second and third hydrogen bond acceptors, wherein:

(a) the relative positions of centroids of the above features are defined by the following Cartesian coordinates in Å:

(i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;

(ii) second hydrogen bond acceptor, 5.08, 2.23 ,0.0;

(iii) third hydrogen bond acceptor, 7.15, 0.80, 0.00;

(iv) first hydrophobic group, –1.52,-3.06, -0.23;

(v) second hydrophobic group, 9.07, 0.00, 0.00; and

(b) tolerances in the positions of the hydrophobic groups and the hydrogen bond acceptors are ± 1.0 Å and ± 1.5 Å respectively.

19. The compound of claim 18, wherein the first hydrophobic group contains a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a 5- or 6-membered monocyclic aromatic group which may contain one or more heteroatoms and which may be 4-substituted or 3,4-disubstituted, but which is of width (including substituents) less than 4.0 Å.

20. The compound of claim 19, wherein the pi-system of the aromatic ring is electron rich.

21. The compound of claim 19, wherein first hydrophobic group, is linked by a first linker chain which is three atoms long to a first 5- or 6-membered ring of the scaffold, the first linker chain atom adjacent to said first scaffold ring forming part of the first hydrogen bond acceptor.

22. The compound of claim 21, wherein the chain has a methylene group located adjacent to the hydrophobic group.

23. The compound of claim 21, wherein the scaffold further comprises a second scaffold ring fused to the first scaffold ring at locations two and three ring atoms distant from the junction between the first scaffold ring and the first linker chain, and the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is two positions distant from said junction forms part of the second hydrogen bond acceptor.

24. The compound of claim 23, wherein the atom of the second scaffold ring adjacent to the atom of the first scaffold ring that is three positions distant from said junction has a substituent which is a single atom or is a methyl group.

25. The compound of claim 23, wherein the second scaffold ring is 6-membered and the atom of the second scaffold ring that is two positions distant from the atom that forms part of the second hydrogen bond acceptor forms part of the third hydrogen bond acceptor.

26. The compound of claim 23, wherein the second scaffold ring is 6-membered and a third scaffold ring is fused to the second scaffold ring at those atoms of the second scaffold ring which are two and three positions distant from the atom that forms part of the second hydrogen bond acceptor, an atom of the third scaffold ring forming part of the third hydrogen bond acceptor.

27. The compound of claim 18, wherein the second hydrophobic group is a 5- or 6-membered aromatic ring which may contain one or several heteroatoms, a bicyclic ring system containing between 8 and 10 atoms and which may contain one or several heteroatoms, or a planar saturated or unsaturated system.

28. A ligand that binds allosterically to MMP-13 and that comprises a scaffold, first and second hydrogen bond acceptors and first and second hydrophobic groups connected by side chains to the scaffold, a cyclic structure forming part of the scaffold being located between the first and second hydrogen

bond acceptors, and the hydrogen bond acceptors and hydrophobic groups being arranged so that when the ligand binds to MMP-13:

the first and second hydrogen bond acceptors bond respectively with Thr245, Thr 247;

the first hydrophobic group locates within the S1' channel; and

the second hydrophobic group is relatively open to solvent.

29. A ligand that binds allosterically to MMP-13 and that comprises a scaffold, first, second and third hydrogen bond acceptors, and a hydrophobic group connected by a side chain to the scaffold, a cyclic structure forming part of the scaffold being located between the first and second hydrogen bond acceptors, and the hydrogen bond acceptors and hydrophobic group being arranged so that when the ligand binds to MMP-13:

the first, second and third hydrogen bond acceptors bond respectively with Thr245, Thr 247 and Met 253; and

the first hydrophobic group locates within the S1' channel.

30. A ligand that binds allosterically to MMP-13 and that comprises a scaffold, first, second and third hydrogen bond acceptors, and first and second hydrophobic groups connected by side chains to the scaffold, a cyclic structure forming part of the scaffold being located between the first and second hydrogen bond acceptors, and the hydrogen bond acceptors and hydrophobic groups being arranged so that when the ligand binds to MMP-13:

the first, second and third hydrogen bond acceptors bond respectively with Thr245, Thr 247 and Met 253;

the first hydrophobic group locates within the S1' channel; and

the second hydrophobic group is open to solvent.

31. A ligand that binds allosterically to the S1' and S1" pockets of MMP 13.

32. The ligand of claim 31, wherein the S1" pocket is defined by amino acid residues from Tyr246 to Pro255.

33. A pharmaceutical composition comprising a compound as claimed in claim 1 claim and a pharmaceutically acceptable excipient.

34. A pharmaceutical composition comprising a compound as claimed in claim 9 and a pharmaceutically acceptable excipient.

35. A pharmaceutical composition comprising a compound as claimed in claim 18 and a pharmaceutically acceptable excipient.

36. Use of a compound according to claim 1 for the preparation of a medicament for the treatment of a disease by inhibition of MMP-13.

37. Use of a compound according to claim 1 for the manufacture of a medicament for the treatment of any of arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, peridontal disease, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration or cancer.

38. A method of treatment of any of arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, peridontal disease, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration or cancer which comprises administering to a patient an effective amount of a compound as defined in claim 1.

39. Use of a compound according to claims 9 for the preparation of a medicament for the treatment of a disease by inhibition of MMP-13.

40. Use of a compound according to claim 9 for the manufacture of a medicament for the treatment of any of arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, peridontal disease, inflammatory bowel disease,